REMARKS

Claims 1, 2, 4, 10-14, 16, 18-20, 22, 23, 32-34, 36, 44, 47, 49, 58, 60-62, 64, 65, 68, 88 and 89 were pending in the application. Of these, claims 1, 2, 4, 10-14, 16, 18-20, 22, 23 and 32-34 had been withdrawn from consideration and remain so.

Claims 36, 44-47, 49, 58, 60-62, 64-65, 68, 88-89 were examined and rejected.

Applicants thank the Examiner for withdrawal of the rejection under 35 USC § 112, 1st paragraph (lack of written description) and all prior art rejections.

The following claims are being amended

- Claim 36: *inter alia*, is limited to the scope of claim 49 (to SIRS as the inflammatory condition).
- Claim 60 and 61 : "inflammatory condition" is explicitly amended to "SIRS" (even though that limitation is already present by virtue of dependency (direct or indirect) from amended claim 36.
- Claim 68: a clerical omission and a spelling error are corrected ("is drotrecogin").
- Claim 89 is canceled and replaced by new claim 90 to avoid the "awkwardness" of reading the claimed in marked up form). It is rewritten as a "method of identifying a human subject at risk of death in whom treatment with activated protein C decreases said risk…" instead of "A method of administering activated protein C to a selected human subject…" Additionally, the claims indicates the precise risk genotypes by nucleotide alternatives at given position.

Cancelations: Active claims 49, 58, 62, 64, 65 and 89 are canceled without prejudice or disclaimer.

New Claims: claims 90 (as noted), 91 (adding a limitation to claim 90) and claims 92 and 93, depending from claim 36, directed to septic shock and sepsis.

All the amendments and new claims find support in the original claims and specification. No new matter is added, and entry of these claims is requested.

As a result of the foregoing actions, claims 36, 44-47, 60-61 68, 88 and 90-93 remain in are under active examination while claims 1, 2, 4, 10-14, 16, 18-20, 22, 23 and 32-34 remain withdrawn. Applicants note that the highest number of claims paid for in this application were 46 total (8 independent) so that no extra claim fees are due.

I. OBJECTION TO SPECIFICATION

The Action maintained the objection to the specification due to lack of continuing data in the first paragraph as no Application Data Sheet (ADS) had yet been filed.

Applicants are submitting an ADS herewith to correct this.

II. MAINTAINED REJECTIONS UNDER 35 USC § 112, 1ST Paragraph

A. The Rejections

All active claims (36, 44-47, 49, 58, 60-62, 64-65, 68, 88-89) were rejected due to lack of enablement. The specification was considered to enable a method of treating SIRS in a human subject by selecting a subject that is homozygous for the C allele or heterozygous for the C/T alleles at position 4732 of SEQ ID NO: 1 and administering activated protein C to the subject.

However, the Office maintains that the application does *not* reasonably enable:

(1) a method of treating an inflammatory condition in a human subject that comprises:
   (a) selecting a human subject having a risk genotype for said inflammatory condition in his protein C sequence wherein the risk genotype is located at a polymorphic site at position 4732 of SEQ ID NO: 1 and
   (b) administering activated protein C to the subject selected in (a), wherein the inflammatory condition is SIRS or

(2) a method of administering activated protein C to a selected human subject comprising: administering activated protein C to a subject with a risk genotype who is selected for the administration on the basis of a protein C characterized by a polymorphic site at position 4732 of SEQ ID NO: 1.

All active claims (but 89) are allegedly drawn broadly to a method of treating an inflammatory condition in a human subject in need thereof. The claim steps comprise

   (a) selecting a human subject having a risk genotype for the inflammatory condition in his protein C sequence wherein the risk genotype is located at position 4732 of SEQ ID NO: 1 and
   (b) administering activated protein C to the subject selected in (a) wherein the inflammatory condition is SIRS.

As stated in the Action, claim 89 is broadly drawn to a method of administering activated protein C to a selected human subject comprising: administering activated protein C to a subject with a risk genotype who is selected for administration on the basis of a protein C characterized by a polymorphic site at position 4732 of SEQ ID NO:1.

The Action points to the definition in the specification (at page 34) of a ***risk genotype*** as "an allelic variant (genotype) at one or more polymorphic sites within the Protein C sequence that is indicative of a decreased likelihood of recovery from an inflammatory condition or an

increased risk of having a poor outcome." The claims encompass selecting a subject having a polymorphic variant in his protein C gene that is associated a decreased likelihood of recovery from an inflammatory condition or an increased risk of having a poor outcome.

Claims 36 and 89 allegedly define the polymorphic variant **only** in terms of the position in SEQ ID NO:1, which encompasses detecting any allele (*i.e.*, A, T, C or G) at position 4732. Only claims 58 and 62 recite specific alleles at this position: in claim 58 the risk genotype is 4732C and in claim 62, the genotype for decreased risk is 4732T. However, according to the Office, the claims do not establish whether these alleles need to be in homozygous or heterozygous form to be associated with this risk.

As stated in the Action, the nature of the claims requires a reliable association between the identity of the nucleotides present at position 4732 of SEQ ID NO: 1 and a decreased likelihood of recovery from SIRS or an increased risk of having a poor outcome. Example 2 teaches an association between the 4732C and altered survival and organ dysfunction in critically ill adults with SIRS. Specifically, in humans with SIRS, the C allele at 4732 (in **heterozygous or homozygous** form) is correlated with decreased survival and increased multiple organ dysfunction.

Example 4 is said to show whether or not treatment with activated protein C (XIGRIS) can reduce organ dysfunction in subjects who have sepsis and who have a risk genotype of protein C such as 4732C. The 28 day survival rates for patients who were **CC/CT** at 4732 were compared to patients who were TT at 4732**,** with and without XIGRIS treatment. The results indicated that XIGRIS treatment increased survival (compared to no treatment) of patients who were CT/CC at 4732 (Fig 7) but that XIGRIS treatment had virtually no effect on survival rate over 28 days in patients who were TT at position 4732. The Examiner concluded from this that specification enables a method of treating SIRS in a human subject, by selecting a subject who is **homozygous for C or heterozygous for C/T alleles** at 4732 and administering activated protein C to that subject. However, the specification allegedly does not enable the claims as they were broadly written. For example all findings in the specification were limited to SIRS patients yet the claims encompass other types of inflammatory conditions, namely, sepsis and septic shock.

{Applicants disagree with the foregoing as discussed below)

The Action goes on to contend *(in error)* that the claims continue to encompass human **and non human** subjects while the disclosure is limited to humans.

Finally the specification allegedly teaches that only in human subjects with SIRS is the **C** allele at 4732 (in heterozygous or homozygous form) correlated with decreased survival and increased multiple organ dysfunction. However the claims allegedly encompass the detection of

any allele (A, T, C or G) at 4732. The claims do not state which allele is associated with risk and whether or not this allele needs to be in homozygous or heterozygous form to be associated with the risk.

Despite the admitted **high** level of skill in this art, the Action contends that the level of unpredictability in making an association between any particular polymorphism and a phenotype is "even higher." The Action give the example that it is unpredictable whether results obtained in SIRS patients can be extrapolated to other inflammatory conditions. The *genus* of inflammatory conditions is said to be "quite large" and each condition allegedly has its own pathology and etiology. However, Applicants' teachings are allegedly limited to an association between the T4732C mutation and altered survival and organ dysfunction in SIRS patients only. Given the alleged differences in the causes and effects of each type of inflammatory condition, the Office believes that one cannot extrapolate results from SIRS subjects to those with "any type of inflammatory condition."

The Action states that the specification teaches an association of only two variants in the protein C gene, namely at positions 4732 and 4800 (of SEQ ID NO:1) with altered survival and organ dysfunction in critically ill adults with SIRS. The Office believes that undue experimentation would be needed to determine if such variants are also associated with altered survival and organ dysfunction in critically ill adults with other types of inflammatory disease (such as sepsis or septic shock). The Action asserts that even after such extensive experimentation, there would be no assurance that such an association would be found. And if an association were found, then even more experimentation would be needed to determine if individuals with sepsis or septic shock also had an improved response to activated protein C therapy. Such "random trial by error experimentation" is considered undue and highly unpredictable; in other words, the specification only provides an invitation to experiment.

In light of the factors discussed above (in view of the *Wands* factors), the Office concluded that the indicated claims are not enabled because undue experimentation would be required to make and use the invention to the full scope of the claims.

B. Applicants' Response

(1) Human vs. Any Subject

The Office continues to maintain that claim 36 and certain dependent claims are drawn to "all subjects," human and non-human, whereas the application is said to enable only human subjects. The Examiner appears to have overlooked the fact that all claims that recited "subjects" had already been limited to humans. Nonetheless, the term "human" has now been inserted in

several additional locations before "subject" (even though not necessary for it to be clear) to make this even more emphatic.

(2) Scope of Inflammatory Conditions

Applicants continue to disagree with the Office's position regarding the nonenablement of sepsis and septic shock and present two further arguments below.

(A) First Argument

The Office Action acknowledges that the claimed method **is** enabled for treatment of SIRS (*e.g.*, Office Action at page 4 para. 7). However, the Office continues to make distinctions between both "sepsis" and "septic shock" from "SIRS" which Applicants believe to be mistaken. For example, at page 9, para. 8, the Action states, incorrectly, that "sepsis and septic shock are **distinctly different from** SIRS" (emphasis added).

The definitions for SIRS, sepsis and septic shock appear in the specification at page 52, lines 1-12 (using pagination from the PCT application as originally filed). SIRS is defined as a broad category which *includes* both septic and non-septic systemic inflammatory responses (*i.e.*, SIRS). The septic systemic inflammatory responses specifically *include* sepsis and septic shock. Furthermore, SIRS is "further defined according to American College of Chest Physicians guidelines (see Bone *et al.*, reference made of record in prior Response) as the presence of two or more of

(i) temperature >38°C or <36°C,
(ii) heart rate >90 beats per minute,
(iii) respiratory rate >20 breaths per minute, and
(iv) white blood cell count >12,000 cells/m^3 or <4,000 cells/mm^3,

which essentially requires that a patient have two or more of the SIRS criteria (*i.e.*, of (i)-(iv) above) in order to have SIRS.

The Office's above statement that "sepsis and septic shock are distinctly different from SIRS" appears to be based on erroneous reasoning by which sepsis and septic shock are described as "distinct from SIRS." Sepsis and septic shock are both ***encompassed*** by SIRS. ("Sepsis" is defined as the presence of at least two "SIRS" criteria and a known or suspected source of infection; "septic shock" is defined as sepsis plus one new organ failure by Brussels criteria plus need for vasopressor medication. See specification at page 52, lines 10-12). SIRS is a syndrome that encompasses individual "member" conditions like sepsis and septic shock. Given the foregoing, Applicants do not understand how sepsis and septic shock can be considered to be "distinctly different from SIRS."

Analogizing to the Office's reasoning here, one could characterize a "banana" and an "apple" as being encompassed by the term "fruit" in the same way that sepsis and septic shock are encompassed by SIRS (because they manifest two or more of the SIRS criteria). The Office's position, however, is analogous to saying that a banana is distinctly different from a fruit.

Claim 36 (and therefore, most of its dependent claims) have been amended to remove sepsis and septic shock and to recite the inflammatory condition as being SIRS. However, these two species are added in the form of new dependent claims 92 and 93 to reflect the fact that sepsis and septic shock are indeed species within the broader genus/category SIRS.

(B) Second Argument

The patients in Example 4 who had improved responses to therapy with activated protein C (*i.e.*, XIGRIS™) "were critically ill patients with severe sepsis" (page 90 - line 8). So Applicant cannot but disagree with the Office's insistence that the findings in the specification are somehow "limited to SIRS."

The Examiner read claim 89 as including "all conditions" making it allegedly even broader than claim 36 in this regard. Note that claim 36 was formerly limited to the inflammatory conditions of sepsis, septic shock or SIRS. The Office, as discussed above, contends that enablement is provided only for SIRS. As further support for their disagreement with this position, Applicants submit herewith as Appendix 1 the "drug label" for activated protein C known as "Drotrecogin alfa (activated)" - the trade name of which is XIGRIS™. At page 4 ("Indications and Usage") , this document shows that the drug is approved for use in the treatment of "severe sepsis" (underscored in document).

(3) Specificity of Naming of Risk Alleles at Particular Positions

The Action indicates the Office's requirement that the claims must recite the specific alleles (*i.e.*, T or C) when reference is made to risk alleles, *etc.* Similarly, the Action indicates that, where appropriate, the claims should recite whether an allele is in heterozygous or homozygous form, noting for example, that both the heterozygous or homozygous "C" alleles at position 4732 are predictive of risk (see also Example at page 92 of the application). Claim 36 and, where needed, its dependent claims, have been amended accordingly to make both these types of changes. New claim 90 (replacing rejected claim 89) does the same.

(4) Further Discussion of Claim 90 (replacing claim 89) and Claim 91

In addition to the aspects of claim 90 already discussed above, Applicants note again the focus of the claim has been modified from "A method of administering activated protein C to a selected human subject…" which did not really capture the essence and purpose of the claim, to "A method of **identifying** a human subject at risk of death in whom treatment with activated protein C decreases said risk…".

Also added is the first "selection" step, that involves selecting human subjects who have an APACHE II score of ≥ 25, which is an indicator of high risk of death. Thereafter, subjects are selected on the basis of their risk genotype in the protein C (and the EPCR) gene. The claim ends with the statement "thereby identifying said subject."

Claim 91 focuses in on one form of activated protein C (treatment with which decreases the risk of death), namely, drotrecogin alfa activated (*i.e.*, XIGRIS™).

(5) Species Not Yet Examined

In view of the election of species made, the claims continue to recite the additional polymorphisms (*i.e.* nonelected species) so that these can be considered and examined once the various issue of patentability have been resolved as to the elected species. Because the present amendments are believed to overcome the remaining rejections, the additional species are ready for examination and allowance as well.

III. CONCLUSION

Applicants respectfully request entry of the foregoing amendments and remarks, none of which are believed to raise new issues of patentability and therefore would be proper after a final rejection (even were an RCE not filed here). Applicants believe that they have overcome all the pending grounds for rejection. The present claims are now in condition for allowance which is earnestly solicited. **Examiner Shaw is respectfully requested to phone the undersigned to discuss any remaining issues that may advance this case rapidly to allowance.**

Respectfully submitted,

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